REMARKS

Applicants thank the Examiner for courtesy extended to Applicants during the telephone interview conducted with the undersigned on December 23, 2002.

In the Final Action dated March 20, 2002, claims 1-5 and 24-32 are pending and are under consideration. Claims 1-5 and 24-28 are rejected under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb (U.S. Patent 5,869,242). Claims 1-7 and 24-30 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Sutherland et al. (U.S. Patent 5,985,619). Claims 1-5, 10, 14 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster (U.S. Patent 6,074,823). Claims 1-5, 8-9, 11-13, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli (U.S. Patent 5,808,300). Claims 1-5, 10, 14, 16 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in the view of Sutherland et al. Claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Caprioli and further in view of Sutherland et al. Claims 1-5, 10, 14, 16-18 and 24-28 are rejected under 35 U.S.C. §103 (a) over Kamb in view of Koster and further in view of Caprioli.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1-5 and 24-28 are rejected under 35 U.S.C. §102 (e) as allegedly anticipated by Kamb (U.S. Patent 5,869,242).

It is observed that claims 1-5 and 24-28 are directed to methods of detecting a difference of one or more nucleotides between a nucleic acid molecule and a reference nucleic acid molecule. The claimed methods involve subjecting the test nucleic acid to base-specific

cleavage and separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS to produce a fingerprint.

Applicants reassert that Kamb's disclosure relates to a method of mutation detection based on analysis of nucleic acid molecules by mass spectrometry. Kamb does not adequately teach a method of detection that employs base-specific cleavage of a test nucleic acid molecule, as instantly claimed. In one instance, Kamb discloses cleaving the amplified fragment of a test molecule with a restriction enzyme prior to mass spectrometry. However, restriction enzymes act upon specific strings of sequences, i.e., cleavage by a restriction enzyme is sequence specific. It is abundantly clear to those skilled in the art that, unlike base-specific cleavage by an agent (e.g., uracil-N-glycosylase) that cleaves a nucleic acid molecule at each occurrence of a particular base, cleavage by restriction enzymes is <u>not</u> base-specific.

Accordingly, Applicants respectfully submit that Kamb does not teach the claimed invention. The rejection under §102(b) based on Kamb is therefore overcome. Applicants further note that the Examiner indicated during the telephone interview on December 23, 2002 that the §102(b) rejection based on Kamb would be withdrawn upon the filing of the Request for Continued Examination.

With respect to the rejections raised under §103, Applicants observe that all these rejections are based on combination of Kamb and one or more secondary references. Applicants reassert that Kamb does not teach a method of mutation detection using base specific cleavage.

The Examiner argues in the Advisory Action that even if Kamb does not teach base specific cleavage, Sutherland et al. clearly teach base-specific cleavage and provides excellent motivation to combine the references.

In the first instance, Applicants observe that the Sutherland et al. reference is not relied upon in some of the §103 rejections, including the rejection of claims 1-5, 10, 14 and 24-28 based on Kamb in view of Koster, the rejection of claims 1-5, 8-9, 11-13, 24-28 and 31-32 based on Kamb in view of Caprioli, and the rejection of claims 1-5, 10, 14, 16-18 and 24-28 based on Kamb in view of Koster and further in view of Caprioli. Therefore, the Examiner's argument that Sutherland et al. provide teachings not provided by Kamb is not applicable to these rejections. Accordingly, it is respectfully submitted that these rejections are improper and withdrawal thereof is respectfully requested.

As to the remaining §103 rejections based on at least Kamb and Sutherland et al., Applicants respectfully submit that Sutherland et al. merely teach the use of uracil-N-glycosylase to cleave primer dimers prior to a PCR reaction in order to reduce non-specific amplification products. Sutherland et al. do not provide any teaching or suggestion for the use of uracil-N-glycosylase in cleaving nucleic acid molecules to produce fragments which are separated based on mass for detecting mutations.

During the telephone interview, the Examiner insisted that the teaching of Sutherland et al. with respect to uracil-N-glycosylase-mediated cleavage of nucleic acid molecules and with respect to the commercial availability of uracil-N-glycosylase, provides sufficient motivation for those skilled in the art to modify the method of Kamb in order to reach the instant invention.

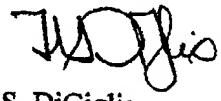
Applicants respectfully submit that the rejection of claimed subject matter under 35 U.S.C. §103 in view of a combination of prior art references requires that the suggestion to carry out the claimed invention must be found in the prior art, *not in Applicant's disclosure*. In re Vaeck, 947 F.2d 488, 492, 20 U.S.P.Q. 1438, 1442 (Fed. Cir. 1991). The fact that references can be combined does not make the combination obvious unless the prior art also contains something

to suggest the desirability of that combination. In re Imperato, 486 F.2d 585 179 USPQ 730 (C.C.P.A. 1973); In re Sernaker, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). In the instant case, Sutherland et al. at most suggest the desirability of using uracil-N-glycosylase to cleavage primer-dimers prior to a PCR reaction in order to reduce non-specific amplification. Sutherland et al. do not suggest any desirability of using uracil-N-glycosylase to cleave nucleic acid molecules for detecting mutations in such molecules, i.e., Sutherland et al. does not suggest the desirability of the combination of its own teaching and that of Kamb.

Therefore, Applicants respectfully submit that there is no proper teaching or suggestion in Kamb or Sutherland to combine the teachings of the two in order to arrive at the claimed invention. Accordingly, the §103 rejection of claims 1-7 and 24-30 based on Kamb in view of Sutherland et al., the rejection of claims 1-5, 10, 14, 16 and 24-28 based on Kamb in view of Koster and further in the view of Sutherland et al., and the rejection of claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 based on Kamb in view of Caprioli and further in view of Sutherland et al., are overcome. Withdrawal of these rejections is respectfully submitted.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Please amend the claims as follows:

10. (Amended) A computer program which controls a method of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule, said method comprising subjecting the test nucleic acid molecule to base specific cleavage to generate oligonucleotide fragments, separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS or other equivalent procedure to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment and identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure, wherein the presence of an altered peak is indicative of a difference of one or more nucleotides in said tested nucleic acid molecule.

24. (Amended) A method for identifying or locating a mutation in one or more bases in a target nucleic acid molecule, comprising subjecting the target nucleic acid molecule to base specific cleavage to generate oligonucleotide fragments, separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS or other equivalent procedure to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment, and identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure, wherein the presence of an altered peak is indicative of a mutation in one or more bases in said target nucleic acid molecule.

REMARKS

In the Office Action dated August 20, 2001, claims 1-18 and 24-32 are under consideration. Claims 19-23 are withdrawn from consideration as drawn to non-elected